DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

VIA FEDERAL EXPRESS

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Warning Letter

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Harvard University – Massachusetts Institute of Technology
Biomedical Engineering Center (MIT-BMEC)
Thomas D. and Virginia W. Cabot Professor Health
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77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Dear Dr. Edelman:

This Warning Letter informs you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your nonclinical testing facility. This letter also requests that prompt corrective actions are implemented in response to the violations cited. Ms Karen E. McNabb-Noon and Dr. Kristina M. Joyce, investigators from FDA's New England District Office conducted the inspection during January 13 through January 30, 2004. The purpose of the inspection was to determine whether activities and procedures of the testing facility identified as Biomedical Engineering/Experimental Cardiovascular Interventional Laboratory at Brigham and Women's Hospital (BMECI) and the Edelman Laboratory of the Biomedical Engineering Center at Massachusetts Institute of Technology-Histology Unit (MIT-HU) complied with Title 21, Code of Federal Regulations, (CFR), Part 58 – Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies. These regulations apply to consulting laboratories, contractors, and grantees that conduct nonclinical laboratory studies that support or intended to support applications for research or marketing permits for products regulated by FDA.

Ms. McNabb-Noon and Dr. Joyce reviewed both the records of your organization and personnel to conduct nonclinical laboratory studies, including the protocols for three nonclinical laboratory studies:

1. [redacted]
   Study Number [redacted]
2. [redacted] Study Number [redacted]
3. [redacted] Study Number [redacted]

During the inspection and our review of the inspection report prepared by the New England District Office revealed violations of the requirements of 21 CFR Part 58.

At the close of the inspection, Ms Karen McNabb-Noon and Dr. Kristina M. Joyce presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations in the presence of [redacted] and [redacted]. The violations noted on the Form FDA 483 and our subsequent review of the inspection report are discussed and summarized below.

1. **The testing facility management failed to establish standard operating procedures (SOPs) adequate to ensure the quality and integrity of the data generated during the course of a study, to limit unauthorized and undocumented procedural deviations, and to establish controls to ensure accountability of SOPs (21 CFR 58.63(b), 58.81(a), 58.81(b), 58.81(d), 58.83, 58.90(i), and 58.107)**

Examples of this failure include but are not limited to the following:

- There is no suitable SOP to track the handling of test and control articles that would preclude error in the receipt and distribution of each batch documented.
- There are no SOPs for the laboratory tests specifically required by study protocols.
- There are no SOPs to determine the acceptability of reagents and solutions.
- There is no suitable SOP for the collection and handling of specimens shipped to contractors for analyses.
- There is no suitable SOP established for the testing and maintenance of autoclave located in the surgical room.
- There is no suitable SOP established to address the inspection and maintenance of the defibrillator located in the operating room of the surgical unit.
- Deviations in a study from SOPs were not always authorized by the study director and documented in the raw data.
- A historical file of SOPs and all revisions including dates of such revisions was not maintained.

2. **Failure to conduct studies per approved protocol (21 CFR 58.130)**

Examples of this failure include but are not limited to the following:

- In Study [redacted] the Study Director did not adhere to the protocol by executing procedures outside of specific requirements for temperature and humidity.
- In Study [redacted] the Study Director did not adhere to the protocol by executing procedures outside of specific requirements for temperature and humidity.

3. **Failure to retain reserve samples from each batch of test and control articles from studies longer than four weeks (21 CFR 58.105(d))**

The testing facility does not maintain reserve samples for required studies. It was determined that the testing facility did not retain reserve samples for Study [redacted] and in, at least eight other studies conducted since 2001.

4. **Failure to prepare the reporting of nonclinical laboratory study results (21 CFR 58.185)**

Examples of this failure include but are not limited to the following:

- The final report for Study [redacted] does not indicate the date when the study was initiated.
- The final reports for Studies [redacted], [redacted] and [redacted] do not describe all circumstances that may have affected the quality or integrity of the data.
- The final reports for Studies [redacted] and [redacted] do not have the names of scientists or professionals other than the study director, and the names of all supervisory personnel, involved in the study.
- The final reports for Studies [redacted], [redacted], and [redacted] do not include the signed and dated reports of each individual scientist or professional involved in the study.
- The final reports for Studies [redacted], and [redacted] do not identify the locations of all specimens, raw data, and records to be stored.

5. **Failure to have protocols that clearly contain information to conduct the nonclinical laboratory studies (21 CFR 58.120(a)(7))**

Examples of this failure include but are not limited to the following:

- Protocols [redacted], [redacted], and [redacted] do not contain a description and identification of the diet used in the nonclinical laboratory studies.

We acknowledged your written responses on February 12, March 10, and March 12, 2004 to the Form FDA 483. Your written responses describe the efforts taken by your testing facility management to address and correct violations observed during the inspection. We find that your actions, which include new and revised SOPs, employment and training of key personnel, and dispensing additional resources to critical areas, will provide greater consistency, reliability, and accountability in your GLP program. Other improvements and changes to your GLP program were verbally communicated to our office on May 18-20, 2004. Please provide a status report of the changes proposed and

implemented to date, a timetable of when they will be completed, and an explanation for any rescission of corrective actions proposed in your February 12, March 10, and March 12, 2004, letters.

With regard to your response to the FDA 483, Observation 3 (protocol deviations), we believe that the actions to notify the building maintenance and the study sponsor after each deviation are appropriate. Resolution should be documented in the study records and described in the final report. If the deviations are permanent and they change the requirements described in the approved study protocol, documentation of the changes and the reason for the changes are best accomplished by issuing a formal protocol amendment. If exceptions from laboratory's SOPs apply for the study, then those exceptions should be described in the protocol. In cases where it is impossible to issue an amendment prospectively, an amendment should be issued as soon as possible.

There is a need for personnel to understand GLP requirements; especially the testing facility management. This familiarity helps to assure that the study personnel are aware of the requirements set forth in the regulation which may alleviate future violations. If the testing facility decides to conduct a nonclinical laboratory study subject to GLP requirements, then the management of the testing facility must assure that the nonclinical laboratory study complies with these requirements. Although the testing facility management requires the quality assurance unit to maintain a master schedule, there is no assurance that all nonclinical laboratory studies conducted at the testing facility and subject to this regulation are included in the master schedule.

Additionally, management should address the preparation of the final reports. Reports from professionals and scientists involved in the study should be finalized and included in the report before it is signed and dated by the study director. Any changes in the report must be in the form of an amendment which meets the requirements of 21 CFR 58.185. To avoid the necessity for many report amendments, the report should not be signed by the study director until it has been reviewed by the scientists involved in the study, has been audited by the quality assurance unit, and after all changes and corrections occasioned by that review and audit have been made.

The sponsor should be informed of the noncompliance conducted in the analyses and services directly involved in their sponsored studies. Generally, sponsors are required to report whether nonclinical laboratory studies intended to support an application submitted to FDA were conducted in compliance with Part 58. See e.g. 21 CFR 812.27, 21 CFR 312.23(a)(8)(iii), 21 CFR 314.50(d)(2)(v), and 21 CFR 814.20(b)(6)(i) for Investigational Device Exemptions, Investigational New Drugs, New Drug Applications, and Premarket Approval Applications respectively.

Within 15 days working days, after receiving this letter please provide written documentation of any changes and amendments since March 12, 2004, to address these violations and to respond to the Warning Letter. Failure to respond to this letter and take appropriate action could result in the FDA taking regulatory action without further notice to you. Send your response to: Food and Drug Administration, Center for Devices and

Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2094 Gaither Road, Rockville, Maryland 20850. Attention: Kevin M. Hopson, M.B.A., Consumer Safety Officer.

We are also sending a copy of this letter to FDA's, New England District Office, One Montvale Avenue, Fourth Floor, Stoneham, Massachusetts 02180, and request that you also send a copy of your response to that office.

Please direct all questions concerning this matter to Mr. Hopson at (301) 594-4720, extension 128.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health